Europäisches Patentamt
European Patent Office
Office européen des brevets

Bescheinigung Certificate Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02021810.3

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 02021810.3
Demande no:

Anmeldetag:
Date of filing: 26.09.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Pooger Properties,
Grant Thornton Stonehage Ltd.
P.O. Box 639,
Sir Walter Raleigh House,
48/50 Esplanade
St. Helier,
Jersey,
Channel Islands JE1 4HH
GRANDE BRETAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Combined use of methylphenidate and melatonin for treating attention-deficit hyperactive disorder

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61K31/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

Combined use of methylphenidate and melatonin for treating Attention-Deficit Hyperactive Disorder

The present invention relates a to the combined use of methylphenidate and melatonin for the treatment of attention-deficit hyperactivity disorder ("ADHD") in mammals, including humans. The invention relates also to a pharmaceutical composition comprising methylphenidate and melatonin.

As described in EP-A-0 896 536, ADHD is a condition affecting a significant proportion of children and which is manifest by learning difficulties, restlessness, inability to settle to any task, argumentativeness, low frustration tolerance and aggressive conduct. A traditional method of treating such children was by administration of psycho-stimulant such as methylphenidate.

Methylphenidate, also known under the trademark Ritalin®, is a medication prescribed for individuals (usually children) who have an abnormally high level of activity or attention-deficit hyperactivity disorder (ADHD). According to the U.S. National Institute of Mental Health, about 3 to 5 percent of the general population in the U.S.A. has the disorder, which is characterized by agitated behavior and an inability to focus on tasks. Methylphenidate also is occasionally prescribed for treating narcolepsy.

Methylphenidate is a central nervous system (CNS) stimulant. It has effects similar to, but more potent than, caffeine and less potent than amphetamines. It has a notably calming effect on hyperactive children and a "focusing" effect on those with ADHD.

Recent research at Brookhaven National Laboratory may begin to explain how methylphenidate helps people with ADHD. The researchers used positron emission tomography (PET - a noninvasive brain scan) to confirm that administering normal therapeutic doses of methylphenidate to healthy, adult men increased their dopamine levels. The researchers speculate that methylphenidate amplifies the release of dopamine, a neurotransmitter, thereby improving attention and focus in individuals who have dopamine signals that are weak, such as individuals with ADHD. See, N. Volkow et al., *J of Neuroscience* (2001) 21:RC121:1-5.

While psychostimulants are useful in increasing attention spans, they have major side-effects, including loss of appetite and insomnia and do not deal with the problems of hyperactivity.

The aforementioned EP-A-0 896 536 discloses the use of lofexidine, 2-[α-(2,6-dichlorophenoxy)ethyl-Δ^2-imidazole, in the manufacture of a medicament for treating

ADHD, which reportedly does not incur the same level of side-effects as clonidine. The latter compound (see Hunt *et al.*, Journal of the American Academy of Child Adolescent Psychiatry 24 (1995)) has been shown to be effective in treating ADHD, but it may also cause hypotension and a high level of sedation as a side-effect. It is stated in said EP reference that while a measure of sedation can be useful in the treatment of hyperactive children, it does not assist in increasing attention span.

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone of the pineal gland, a small organ (approx. 100 mg) located in the mid-brain above the third ventricle (A.B. Lerner *et al.*, *J. Amer. Chem. Soc.* 1958; 80:2587). The rate-limiting enzyme for its synthesis, N-acetyltransferase (NAT) is produced only during the night. Night-time values of NAT are more than 100-fold greater than daytime levels. Melatonin is also produced by extra-pineal tissues, that lightens skin color in amphibians by reversing the darkening effect of MSH (melanotropin). Melatonin has been postulated as the mediator of photic-induced anti-gonadotropic activity in photoperiodic mammals and has also been shown to be involved in thermoregulation in some ectotherms and in affecting locomotor activity rhythms in sparrows.

Melatonin, when used experimentally, is synthesised chemically and has been studied extensively in clinical and preclinical trials to examine the effects of the circadian SCN clock (A.J. Lewy *et al.*, *Behav. Brain Res.* 1996; 73:1-2 131-4).

Non-prepublished international patent application PCT/EP02/03317 discloses that melatonin has usefulness in the treatment of ADHD, and provides the use of at least one of melatonin, a melatonin analogue, or a pharmaceutically acceptable salt of melatonin or said melatonin analogue, in the preparation of a medicament for the treatment of ADHD in mammals, in particular human beings.

The present invention is based on the surprising finding that the combined use of methylphenidate and melatonin has a beneficial effect on the treatment of ADHD, which will frequently exceed the effect of the individual active compounds.

Accordingly, the present invention provides the combined use of methylphenidate and melatonin in any form for the treatment of ADHD in mammals, in particular human beings, especially children.

As used hereinafter, unless stated otherwise, the term "melatonin" includes melatonin per se, a melatonin analogue, i.e. a substance exhibiting high affinity for melatonin receptors, or a pharmaceutically acceptable salt of melatonin or a melatonin analogue.

The medicament for the treatment of ADHD comprising the combination of methylphenidate and melatonin as active ingredients is suitably administered to the mammal in the form of a pharmaceutical composition. The administration may be by way of oral or parenteral administration.

The medicament can be administered in conventional form for oral administration, e.g. as tablets, lozenges, dragees and capsules. However, for the administration of the drug to children, which is likely to be its major use, it may be preferred to formulate the composition as an oral liquid preparation such as a syrup, a nasal spray, or a suppository. The medicament can also be administered parenterally, e.g. by intramuscular or subcutaneous injection, using formulations in which the medicament is employed in a saline or other pharmaceutically acceptable, injectable composition.

An amount effective to treat the disorder hereinbefore described depends on the usual factors such as the nature and severity of the disorder being treated, the weight of the mammal, the specific compounds of choice, and considerations and preferences of the prescriber. The amount of active ingredients to be administered usually will be in the range of nanograms to 50 mg or more per dose. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 400 mg such as 2, 5, 10, 20, 30, 40, 50, 100, 200, 300 and 400 mg of the active ingredient. Unit doses will normally be administered once or more than once per day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult, of 1 to 1000 mg, for example 1 to 500 mg, that is in the range of approximately 0.01 to 15 mg/kg/day, more usually 0.1 to 6 mg/kg/day, for example 1 to 6 mg/kg/day.

It is greatly preferred that the combination of methylphenidate and melatonin according to the invention is administered in the form of a unit-dose composition, such as a unit dose oral, such as sub-lingual, rectal, topical or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use. The preparation of such compositions is well known to people

skilled in the art and can be optimized in a routine way without exerting inventive skill and without undue experimentation.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include, mannitol and other similar agents. Suitable disintegrants include starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations further include controlled release formulations which may also be useful in the practice of this invention. The controlled release formulation may be designed to give an initial high dose of the active material and then a steady dose over an extended period of time, or a slow build up to the desired dose rate, or variations of these procedures. Controlled release formulations also include conventional sustained release formulations, for example tablets or granules having an enteric coating.

Nasal spray compositions are also a useful way of administering the pharmaceutical preparations of this invention to patients such as children for whom compliance is difficult. Such formulations are generally aqueous and are packaged in a nasal spray applicator which delivers a fine spray of the composition to the nasal passages.

Suppositories are also a traditionally good way of administering drugs to children and can be used for the purposes of this invention. Typical bases for formulating suppositories include water-soluble diluents such as polyalkylene glycols and fats, e.g. cocoa oil and polyglycol ester or mixtures of such materials.

For parenteral administration, fluid unit dose forms are prepared containing the compound(s) and a sterile vehicle. The compound(s), depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle.

Parenteral suspensions are prepared in substantially the same manner except that the compound(s) is/are suspended in the vehicle instead of being dissolved and sterilised usually by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound(s) of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

The present invention further provides a pharmaceutical composition comprising at least one of melatonin, a melatonin analogue, or a pharmaceutically acceptable salt of melatonin or said melatonin analogue, and a pharmaceutically acceptable carrier. These pharmaceutical compositions may be prepared in the manner as hereinbefore described.

In the treatment of ADHD patients in accordance with the invention, melatonin ~~or a melatonin analogue~~ can be used ~~alone or together~~ with other active materials. The latter materials are preferably chosen such that either their activiy is enhanced, preferably in a synergistic way, or undesired side-effects are suppressed by melatonin ~~and/or its analogue~~. For example, melatonin ~~or its analogue~~ which can be used in conjunction with ~~the medicament~~ additionally contains one or more substances selected from the group of stimulants, hormones, analogues of such hormones, phyto-hormones, analogues of such phyto-hormones like phyto-estrogen, and anti-oxidants like phyto-vitamins C and E, flavonoids.

Preliminary investigations show the following dose rates. For the occasional self-treatment of mild insomnia in adults: 0.3 to 3 mg oral or sublingual dosage (PO), in the evening hours approximately 1 to 2 hours before habitual bedtime. May take up to 6 mg PO if needed. For the adjunctive treatment of insomnia related to major depression:

Adults: 5 to 10 mg oral extended release formulations (PO) taken 1 to 2 hours prior to habitual bedtime. In one 4-week placebo-controlled study of 19 patients with major depressive disorder treated with fluoxetine, the sub-group of 10 patients who received concomitant slow-release melatonin at 9 pm for sleep reported significantly improved sleep quality scores versus the patients receiving fluoxetine alone. Melatonin treatment avoided the need for additional sleep medications. No differences in the rates of improvement of depressive symptoms or side effects were reported between the two groups. (Dolberg et al; 1998)

For the treatment of delayed sleep phase syndrome resulting from circadian rhythm disruption, including patients with autism, blindness, Rett's syndrome, or developmental disabilities in adults: Doses of 5 to 7 mg oral immediate release formulations (PO) once daily at bedtime have been used in the blind to entrain circadian rhythms to a 24-hour day. (Sack et al; 1991); in children: Doses of 2.5 to 7.5 mg PO once daily before expected bedtime have been used. The average onset of sleep occurred within 1 hour of melatonin administration. Most children were on concomitant anti-convulsant therapies. Melatonin was administered nightly for up to 4 weeks and appeared to be well tolerated. ~~The long-term effects of chronic melatonin use in pediatric patients are unknown. (Chase & Gidal; 1997, McArthur & Budden; 1998) Although Palm et al (1999) and Jan et al (2000) published reports on children who received melatonin for several years without adverse effects. However, doses administered would, to a large extent, depend upon the method of administration.~~ (*) insert!

Although the invention has been described primarily as a therapy for children, it can also be used for adults, although dosage rates may be different in the case of adults. Adaptation and optimization of dosages can be readily achieved by skilled persons without undue experimentation.

~~While psychostimulants are useful in increasing attention spans, they have major side effects, including loss of appetite and insomnia and do not deal with the problems of hyperactivity.~~

~~Said EP-A-0 890 536 discloses the use of lofexidine, 2-[α-(2,6-dichloro-phenoxy)ethyl-Δ^2-imidazole, in the manufacture of a medicament for treating ADHD, which reportedly does not incur the same level of side-effects as clonidine. The latter compound (see Hunt *et al.*, Journal of the American Academy of Child Adolescent Psychiatry 24 (1995)) ha1s been shown to be effective in treating ADHD, but it may also cause hypotension and a high level of sedation as a side effect. It is stated in said EP~~

Insert 1: (in Dutch, English translation to be provided)
to be in Chapter 6

In Nederland is melatonine evenals in de USA een "over the counter" hormoonproduct, dat in doseringen van 0,1 - 0,3 mg - zonder restrictie kan worden verkocht. Melatonine wordt in wisselende zuiverheid geleverd. Toxische verschijnselen zijn niet beschreven en bij een dosering van 240 mg zijn verbazende responsreacties beschreven (H.R. Lieberman et al., Brain Research (1984) 323: 201-207).

ADHD is een gedragsstoornis, die in 54% van de gevallen gepaard gaat met inslaapstoornissen (D. Efron et al., Pediatrics (1997) 100(4) 662-666. Bij behandeling van ADHD-patiënten met methylphenidaat stijgen de inslaapproblemen tot 64% (A.R. Adesman et al, Pediatrics Clinics North America (1999) 46(5): 945-963. Sommige auteurs schrijven het ADHD-gedrag toe aan onvoldoende slaap (M. Thunström, Acta Paediatrica (2002) 91: 584-592). De meest plausibele hypothese voor een persistief ADHD-syndroom wordt gezocht in een gestoorde prikkeloverdracht (op niveau van Noradrenerga/serotenerga) op meerdere hersenlocaties (o.a. prefrontaal, striatiaal en zelfs cerebellair niveau). Zie M. Mercugliano, Pediatric Clinics of North America (1999) 46:5 831-843.
In een pilot study werd reeds aangetoond, dat melatonine 3 mg een significante verkorting opleverde van de inslaaptijd bij patiënten die met methylphenidaat zijn behandeld (C.-V. Tjon Pian Gi et al., poster presentation, Annual Scientific Meeting European Society for Pediatric Research, September 2002

Insert 1 (contd)

Thans werd gevonden, dat zuiver melatonine 2,5 mg werkzaam is als inslaapmiddel bij met methylphenidaat behandelde ADHD-patiënten met inslaapstoornissen.

De uitvinding is daarom mede gebaseerd op methylphenidaat en melatonine gezamenlijk, ongeacht gelijktijdig of na elkaar worden toegepast voor de behandeling van ADHD bij zoogdieren, i.h.b. mensen, meer in het bijzonder kinderen. Bij voorkeur wordt het melatonine toegediend na de toediening van methylphenidaat.

9.

Claims

1. Use of methylphenidate and at least one of melatonin, a melatonin analogue, or a pharmaceutically acceptable salt of melatonin or said melatonin analogue, in the preparation of a medicament for the treatment of ADHD in a mammal, especially a human being.

2. Use as claimed in claim 1 wherein the melatonin or melatonin analogue is employed in an amount of from 0.005 to 1.00 mg/kg in treating ADHD.

3. Use as claimed in any one of the preceding claims wherein the medicament is formulated as a controlled release preparation.

4. Use as claimed in any one of the preceding claims wherein the medicament is formulated as a solid oral formulation.

5. Use as claimed in any one of the preceding claims wherein the medicament additionally contains one or more substances selected from the group of stimulants, hormones, analogues of such hormones, phyto-hormones, analogues of such phyto-hormones, and anti-oxidants.

6. A method of preventing or treating ADHD disorder in a mammal, in particular a human, which comprises administering to said mammal a therapeutically effective amount of methylphenidate and one of melatonin, a melatonin analogue, or a pharmaceutically acceptable salt of melatonin or said melatonin analogue.

7. A pharmaceutical composition comprising, as active ingredients, methylphenidate and at least one of melatonin, a melatonin analogue, or a pharmaceutically acceptable salt of melatonin or said melatonin analogue, in conjunction with a pharmaceutically active carrier.

8. A pharmaceutical composition comprising as an active ingredient methylphenidate and melatonine, in conjunction with a pharmaceutically active carrier.

Abstract of the invention

The present invention relates to the combined use of methyl phenidate and at least one of melatonin, a melatonin analogue, or a pharmaceutically acceptable salt thereof in the treatment of attention deficit hyperactive disorder (ADHD). Methylphenidate and melatonin or its analogue may be used together or in combination with one or more other active ingredients, and is preferably formulated as a composition for controlled release.